

Metabolic Syndrome in Lean Patients with Polycystic Ovary Syndrome – A Case Control Study

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ABSTRACT:

Metabolic syndrome (MBS) is a common disorder related to visceral obesity and insulin resistance (IR) which is associated with atherosclerosis and cardiovascular (CV) disease. Several factors which affect the prevalence of MBS are obesity, IR and diabetes and polycystic ovary syndrome (PCOS). In this present study, our aim was to assess the metabolic risk factors among lean polycystic ovary syndrome and to find the prevalence of the metabolic syndrome among the PCOS. 24 classical PCOS diagnosed by Rotterdam 2003 Diagnostic criteria and were lean as per WHO criteria and 24 BMI matched, age matched normally menstruating women served as study participants. All of them underwent assessments clinically and by appropriate laboratory tests for the evidence of MBS, as per criteria laid down by Rotterdam 2003 diagnostic criteria. MBS was seen in 8.33% of lean PCOS women though not significantly different from their age and BMI matched controls, but it was 2.02 times than in controls. Among the risk factors dyslipidemia was higher with the prevalence of 70.83%. Our data suggest that all PCOS patients should undergo periodic screening for MBS irrespective of obesity.

Key Words: Metabolic syndrome, Polycystic Ovary Syndrome, visceral obesity, dyslipidemia, fasting blood glucose

INTRODUCTION

Metabolic syndrome (MBS) is a common disorder related to visceral obesity and insulin resistance (IR) which is associated with atherosclerosis and cardiovascular (CV) disease [1, 2]. Several factors affect the prevalence of MBS. These include obesity [3], IR and diabetes [4], and polycystic ovary syndrome (PCOS) [5]. The prevalence of MBS is high, occurring in 31.6% in Indian urban population, prevalence is 31.6 % in men and 39.9% in women [6]. The overall prevalence of MBS appears to be similar between the USA and European countries with reported rates of 23.5% in Spain and 23.9% in Portugal [7], but compared to the prevalence rate in India, it is slightly lower. Among PCOS north Indian women, the prevalence of MBS is very high and is about 46.2% [8]. Prevalence varies among USA PCOS women (43-46%) [9]. Among European women, in Italy it is (8.2%) [10].

Polycystic ovary syndrome was first described by Stein Leventhal in 1935 and became one of the most common endocrinopathy of premenopausal women, with a prevalence estimated at approximately 25% [11] of the Indian population.

It is one of the most frequent causes of infertility. PCOS was initially recognized as a clinical combination of anovulation and hyperandrogenism; now it appears to be a new face of metabolic syndrome [12]. This common medical condition has brought gynecologists, endocrinologists, cardiologists, pediatricians, and dermatologists together [13]. The disorder manifests as obesity, hirsutism, menstrual

disturbances, acne vulgaris, male-pattern baldness, recurrent abortions, infertility, an-ovulation, and psychological and psychosexual morbidity [14]. With the advances and refinement in ultrasound technology, the presence of polycystic appearance of ovaries has increasingly been accepted as an essential part of the diagnosis of this syndrome and ultrasound suggestion of PCOS has recently been introduced as one of the three diagnostic criteria of PCOS in Rotterdam consensus workshop 2003 [15].

Type II Diabetes mellitus (T2DM), which accounts for 90–95% of all diabetes mellitus, is a common metabolic disorder, characterized by combination of IR and insulin secretory defects, occurring in varying proportions [16]. Both T2DM and PCOS are now considered to be two metabolically similar but phenotypically different expressions of the same syndromic continuum with insulin resistance being the common and pivotal link, which may be genetically determined [17]. Women with PCOS are also at increased risk for cardiovascular disease (CVD), given the high prevalence of the metabolic syndrome among them [18]. Many studies have revealed an increase in prevalence of various abnormalities of glucose tolerance in PCOS [19]. It is well recognized that visceral distribution of body fat, common in this syndrome, is of greater consequence to the metabolic effect of insulin resistance than obesity per se. Central obesity and insulin resistance leads to an altered lipolytic response to insulin, with impaired suppression of release of free fatty acids from adipose tissue. An increased flux of free fatty acids from central sites enters the portal circulation, increasing the availability of substrate to the liver for triglyceride production.

Further more, women with the polycystic ovary syndrome exhibit increased activity of hepatic lipase, an enzyme responsible for the conversion of the large lipoprotein particles to smaller, more atherogenic species [19].

The combination of raised triglyceride and decreased high density lipoprotein is strongly linked with cardiovascular disease. Hence an increase in risk of cardiovascular disease due to lipid abnormalities will present in early adult life. Suppression of hyperandrogenism by use of gonadotropin releasing hormones analogue has little effect on insulin resistance or the dyslipidemia, suggesting that the abnormal lipid profile is independent of the raised androgen concentrations [19].

But obesity is not a prerequisite to the development of PCOS, as 50% of PCOS are not obese [20]. Obesity per se is a disease entity, and its association with insulin resistance (IR)/ hyperinsulinemia and impaired growth hormone secretion is well established. Thus assessment of the relative contributions of obesity and PCOS to neuroendocrine – metabolic aberrations and their impacts hyperandrogenism and chronic anovulation are pivotal in the understanding of this complex syndrome. Several studies have reported hyperandrogenemia and hyperinsulinemia with relatively normal leutinizing hormone (LH) levels in obese PCOS whereas higher LH levels with relatively normal insulin levels are more likely in normal weight PCOS [21]. These isolated observations led to the proposal of subsets of PCOS with differing endocrine inputs to the development of ovarian hyperandrogenism. Elevated insulin resistance, oxidative stress, and plasma homocysteine levels and change in serum lipid profile (risk factors for cardiovascular disease) were observed in lean PCOS patients [22]. Thus there appears to be additional genetic and environmental factors influencing lipid metabolism in PCOS women [23]. Therefore studies of prevalence of features of MBS are necessary in both lean and obese women with PCOS.

In an attempt to determine the prevalence of MBS in PCOS, Criteria proposed by the Rotterdam 2003 PCOS concenses [15] was used to diagnose MBS. These criteria require the presence of 3 of 5 common cardiovascular risk factors (increased waist circumference, elevated blood pressure, fasting blood glucose, low serum high-density lipoprotein (HDL)-cholesterol, and increased triglycerides).

Our purpose in this study was to compare the metabolic parameters in lean PCOS with regularly menstruating normal women. We also determined to estimate the prevalence of different components of MBS.

MATERIALS AND METHODS

The study was conducted in the department of physiology, PSG IMS&R after getting clearance from Institutions Human Ethics Committee, and after obtaining informed consent from the study and control group.

The study group consisted of women who presented to the infertility clinics, gynaecologists and family physicians with complaints of dysfunctional uterine bleeding, or infertility and diagnosed to have PCOS by the experts. Diagnosis of PCOS was made with physical findings of hyperandrogenism, Oligo / anovulation and ultrasonography, after exclusion of specific ovarian, adrenal and pituitary disorders, according to Rotterdam 2003 diagnostic criteria [15]. Prevalence of metabolic syndrome is evaluated by the criteria that have been developed for defining a metabolic syndrome [15].

MBS was diagnosed in subjects presenting with at least three out of the following criteria: increased waist circumference (>88 cm), low serum HDL-cholesterol (<50 mg/dl in women), increased serum triglycerides (>150 mg/dl), increased blood pressure (>130/>85 mm Hg) and high fasting blood glucose (>110 mg/dl). Using WHO criteria, MBS was diagnosed in subjects presenting with one major criterion (diabetes, insulin resistance, altered glucose tolerance) plus two minor criteria [obesity (body mass index (BMI) > 30), hypertension, dyslipidemia (assessed by HDL - cholesterol and triglycerides) and microalbuminuria]. We used Rotterdam 2003 criteria for diagnosing MBS.

Subjects

a. Patient group: This group comprised of 24 non-pregnant lean women with PCOS. The sample size was calculated according to the prevalence of the disease in India [11]. The required sample size calculated was 18. During the study period we analysed 24 PCOS for MBS. The patients were categorised as lean as per the WHO criteria [24].

b. Control group: Control group consisted of 24 regularly menstruating (every 27-32days) volunteer medical students, doctors, nurses and staff of the hospital and who were matched for age and BMI.

Our inclusion criteria for the study group included, those aged 16 to 35, women who were not on any medications affecting lipid or carbohydrate metabolism at least for past 2 months.

Our exclusion criteria included, women aged below 16 and above 35, pregnant and lactating women, those who had undergone hysterectomy and those who had

attained menopause, women taking lipid lowering drugs for the past 2 months, women on oral hypoglycemic drugs or insulin sensitizing agents for the past 2 months, women on oral contraceptives and sex steroids for the past 2 months, those who were on current infertility treatment. After selecting the study and control group according to the selection criteria, written informed consent was obtained. All the participants of the control group were in their follicular phase (6-8 days the start of menstruation) and PCOS were amenorrhoeic during data recording.

Antecubital blood sample was taken after atleast 12 hours fasting for the lipid profile. A detailed history taking and a complete physical examination was done and a complete record was obtained for future verification.

Each patient and control received a detailed clinical examination and underwent a relevant laboratory evaluation. The history focused on age, menstrual pattern, fertility status, duration and treatment of PCOS, and other relevant drug history. The physical examination, apart from a general review of the systems, focused on the anthropometry (body mass index and waist circumference).

Anthropometry

Body mass index (BMI)

All the study and control participants were measured for height and weight (wt). Height was measured in cms as the study participants stood in their upright position using the Height measuring scale. Weight was measured using electronic weighing machine. From this BMI was obtained by dividing weight in Kg by square of the height (in meters). According to WHO, BMI less than 25 were graded as normal, about 25-29 were graded as over weight, and more than 30 as obese [24].

Waist circumference (WC)

Waist circumference was obtained by standard measures [25]. Measurement sites were obtained with the subject assuming a standing position and then the points were marked on the subjects. Waist circumference was measured half way between the lower border of the ribs and the iliac crest in the horizontal plane. 2 measurements to the nearest 0.5 cm were recorded. If the variation between the measurements were >2 cms a third measurements was taken. The mean of the 2 closest measurements was calculated. For females waist circumference 80 – 87.9 cms was graded as overweight and ≥ 102 cms as obese. For the entire study population the BMI and WC was obtained.

Resting blood pressure

At the end of 20 minutes of quiet supine rest, blood pressure was recorded in the supine position, using a manual sphygmomanometer (a Novaphone make). Systolic and diastolic blood pressure was measured with a calibrated manometer from the right arm and recorded to the nearest 2mm Hg. Blood pressure was defined as the points of appearance and disappearance of Korotokoff sounds respectively.

Metabolic profile

The fasting blood sample was taken to get the fasting blood glucose and fasting serum lipid profile and was analysed using SEAC SLIM AUTO ANALYSER, Italy. Blood glucose was determined using glucose oxidase method. Total cholesterol was determined using CHOD-POD i.e., cholesterol oxidase and peroxidase method (enzymatic colorimetric method). Triglycerides were determined by the method based on the enzymatic hydrolysis of serum or plasma triglycerides to glycerol and free fatty acids by lipoprotein lipase and then using glycerophosphate oxidase and peroxidase enzymes (enzymatic colorimetric method). HDL – C was determined using cholesterol esterase method following selective precipitation of Apolipoproteins B containing lipoproteins with a polyanion solution.

Statistical analysis

The Statistical Package for the Social Science (SPSS 12.1 version for windows) was used for statistical analysis. P value less than 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics of the lean PCOS and control group

Mean \pm SD of age of the PCOS was 22.96 ± 3.96 and the control was 24.21 ± 4.69 . Mean \pm SD of BMI of the PCOS was 22.12 ± 2.56 and the control was 20.86 ± 2.73 . Mean \pm SD of weight of the PCOS was 53.60 ± 8.86 and the control was 51.09 ± 9.31 . There was no significant difference between ages, BMI, weight with P value 0.324, 0.104 and 0.344 respectively. This shows the mean age the PCOS group was less than the controls and the BMI and weight were higher than the controls (Refer table 1). Mean \pm SD of waist circumference of the PCOS was 60.96 ± 15.97 and the control was 76.67 ± 8.00 . There was significant difference of the waist circumference with a p value of < 0.001 (Refer Table 1). Waist circumferences of the PCOS group were less than the controls. (Refer chart 1)

Table 1. Baseline characteristics of the lean PCOS and control group

Parameter	Group	Mean \pm SD	P value
Age	Case	22.96 \pm 3.96	0.324 (NS)
	Control	24.2083 \pm 4.6902	
BMI (Kg / m ²)	Case	22.1238 \pm 2.5603	0.104 (NS)
	Control	20.8592 \pm 2.7254	
Weight (Kg)	Case	53.5992 \pm 8.8614	0.344 (NS)
	Control	51.093 \pm 9.306	
Waist Circumference (cms)	Case	60.9583 \pm 15.971	< 0.001**
	Control	76.667 \pm 7.998	

NS – Not Significant

* – Significant

** – Highly Significant

Table 1 shows that age; BMI and weight of the study and the control group were not significant. But there was a significant difference in waist circumference.

Table 2. Resting blood pressure of the lean PCOS and control group

Parameter	Group	Mean \pm SD	P value
SBP (mm Hg)	Case	107.667 \pm 10.6594	0.682 (NS)
	Control	106.1667 \pm 14.3001	
DBP (mm Hg)	Case	73.5833 \pm 8.7473	0.338 (NS)
	Control	71.0833 \pm 9.1362	

NS – Not Significant

Table 2 shows that the systolic and diastolic blood pressure of the study and the control group was not significant.

Table 3. Comparison of metabolic profile of the lean PCOS and control group

Parameter	Group	Mean \pm SD	P value
FBS	Case	93.59 \pm 18.15	0.011*
	Control	82.16 \pm 10.12	
ST	Case	97.98 \pm 36.44	0.327 (NS)
	Control	107.52 \pm 29.86	
HDL – C	Case	46.66 \pm 11.01	0.968 (NS)
	Control	46.78 \pm 9.19	

NS – Not Significant

* – Significant

Table 3 shows that the fasting blood sugar was significantly high among the PCOS and controls, but not the triglycerides and HDL-C levels.

Table 4. Prevalence of the metabolic syndrome in lean PCOS

	Metabolic syndrome
Study population	Present
PCOS	8.33%
Control	4.11%
P value	0.5 (NS)

NS – Not Significant

Table 4 shows that the prevalence of Metabolic syndrome was doubled in PCOS though not significantly different.

Table 5. Prevalence of different combinations of the individual components of the metabolic syndrome in lean PCOS

Parameters	Prevalence
Visceral obesity + Hypertension	0 %
Impaired fasting glucose + Visceral obesity	4.17%
Dyslipidemia (Increased triglycerides ,Decreased HDL-C)+ Visceral obesity	20.83%
Hypertension + Impaired fasting glucose	0 %
Hypertension + dyslipidemia	0%
Impaired fasting glucose + dyslipidemia	12.5%

Table 5 shows that dyslipidemia (Increased triglycerides ,Decreased HDL-C) and Visceral obesity had the highest prevalence among the combined risk factors.

Table 6. Prevalence of different individual components of the metabolic syndrome in lean PCOS

Parameters	Prevalence
Visceral obesity	20.83%
Hypertension	0%
Impaired fasting glucose	12.5%
Increased triglycerides	4.17%
Decreased HDL-C	66.67%
Dyslipidemia (Increased triglycerides and Decreased HDL-C)	70.84%

Table 6 shows that among the individual components Dyslipidemia (Increased triglycerides and Decreased HDL-C) had the highest prevalence.

Resting blood pressure of the lean PCOS and control group

Mean \pm SD of SBP of the PCOS was 107.67 ± 10.66 and the control was 106.17 ± 14.30 . Mean \pm SD of DBP of the PCOS was 73.58 ± 8.75 and the control was 71.08 ± 9.14 . There was no significant difference between systolic and diastolic BP with P value 0.682 and 0.338 respectively (Refer Table 2). Mean SBP and DBP were higher than the controls (Refer chart 2).

Comparison of metabolic profile of lean PCOS and control group

Table 3 shows the Mean \pm SD of fasting blood sugar of the PCOS was 93.59 ± 18.15 and the control was 82.16 ± 10.12 . The difference was significant with a p value of 0.0110. On analyzing the fasting lipid profile which included triglycerides (TG), HDL – C, Mean \pm SD of TG of the PCOS was 97.98 ± 36.44 and the control was 107.52 ± 29.86 . Mean \pm SD of HDL – C of the PCOS was 46.66 ± 11.01 and the control was 46.78 ± 9.19 . TG, HDL – C did not show any significant difference with a p value of 0.327 and 0.968 respectively (Refer Table 3). Both the TG and HDL-C were less in PCOS (Refer chart 3).

Prevalence of the metabolic syndrome in lean PCOS

Table 4 shows the prevalence of the metabolic syndrome among lean PCOS. The prevalence of MBS was higher in PCOS group (8.33%) diagnosed as per

the diagnostic Rotterdam 2003 diagnostic criteria compared to 4.11% among the controls (Refer chart 4).

Prevalence of different combinations of individual components of the metabolic syndrome in lean PCOS

Table 5 shows the prevalence of different combinations of the individual components of the metabolic syndrome. The prevalence of visceral obesity and glucose intolerance was high among lean PCOS group (4.17%) compared to the controls (0%). The prevalence of the visceral obesity and dyslipidemia was also higher among the Lean PCOS (20.83%) than the controls (0%). Among the other components glucose intolerance and dyslipidemia was higher in lean PCOS (12.5%) than the controls (0%) (Refer chart 5).

Prevalence of different individual components of the metabolic syndrome in lean PCOS

Table 6 shows the prevalence of different individual components of the metabolic syndrome in lean PCOS. It is seen that prevalence of dyslipidemia was higher (70.84%), among them increased triglycerides were found in 4.17% and decreased HDL-C was present in 66.67%. Prevalence of Visceral obesity is the next parameter where the prevalence was 20.83%. Impaired fasting glucose had a prevalence of 12.5%. There was no hypertensive among our study population. (Refer chart 6)

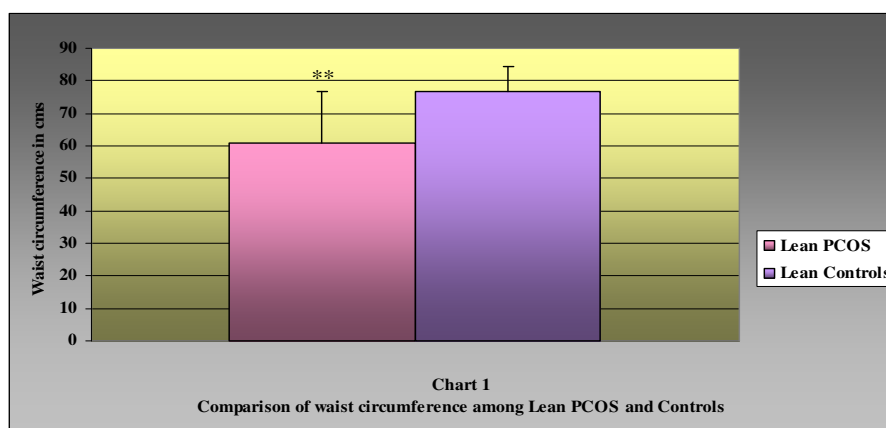


Fig. 1 shows that waist circumference was comparatively higher among controls than PCOS

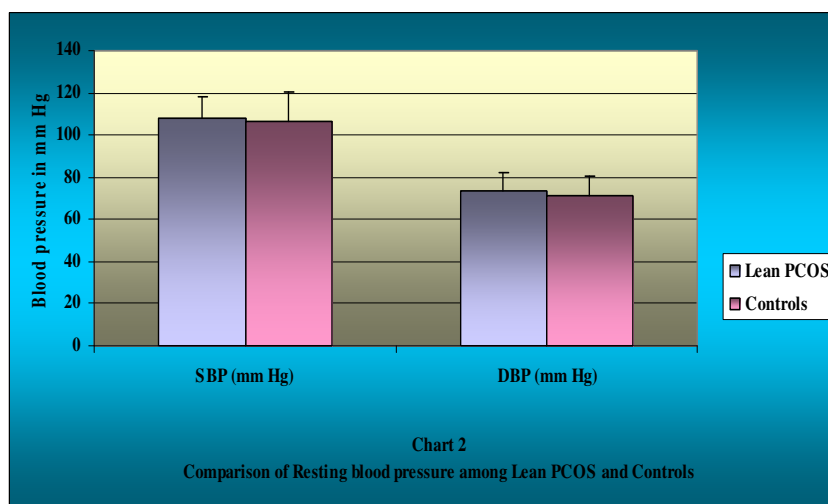


Fig. 2 shows that there was no significant difference in resting blood pressure among PCOS and controls

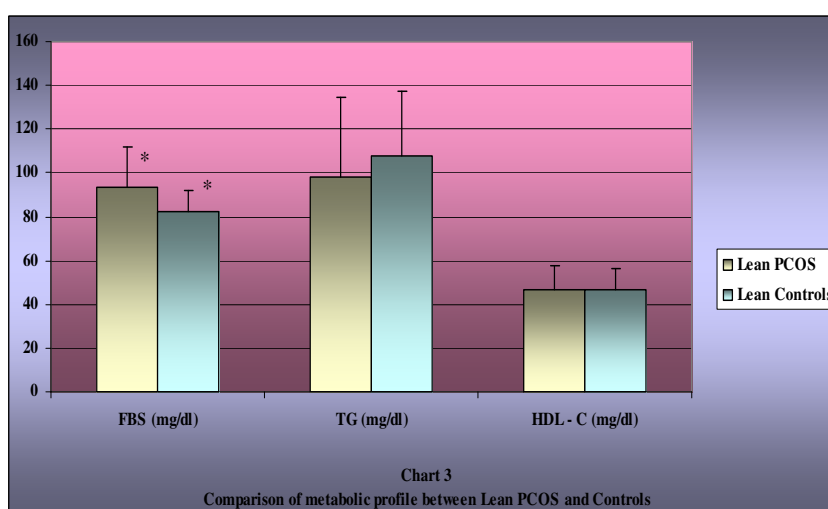


Fig. 3 shows that fasting blood sugar was significantly high among the PCOS and controls, but not the triglycerides and HDL-C levels

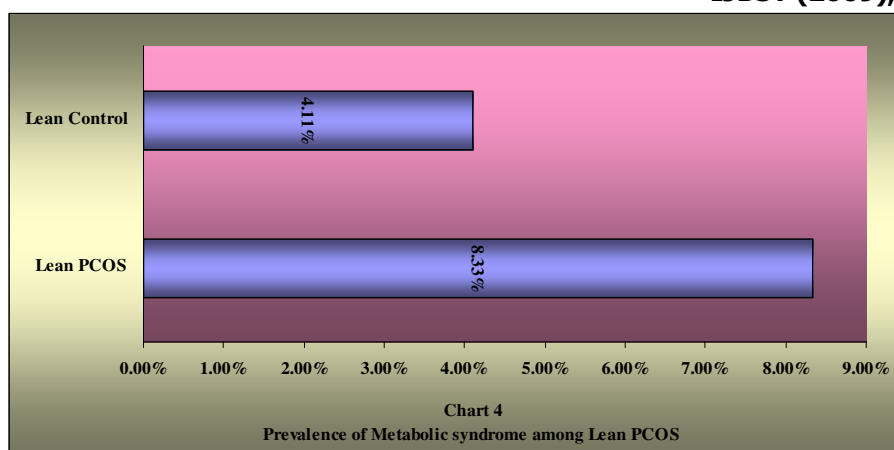


Fig 4 shows that prevalence of Metabolic syndrome was doubled in PCOS than controls ,though not significantly different.

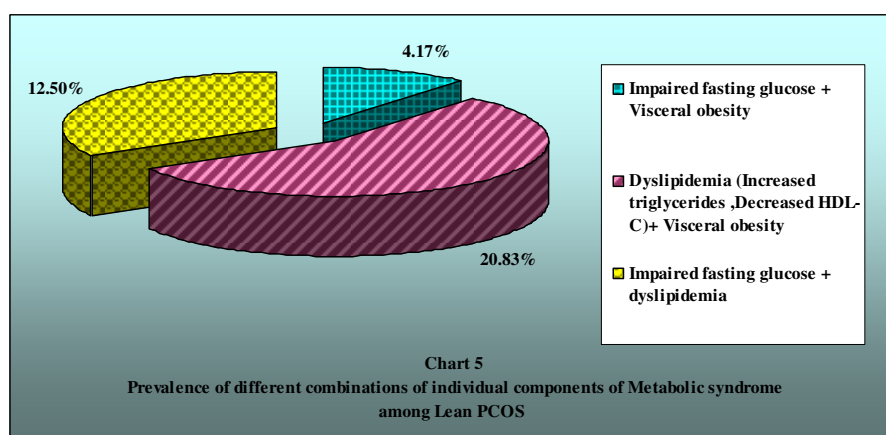


Fig 5 shows that dyslipidemia (Increased triglycerides ,Decreased HDL-C)and Visceral obesity had the highest prevalence among the combined risk factors.

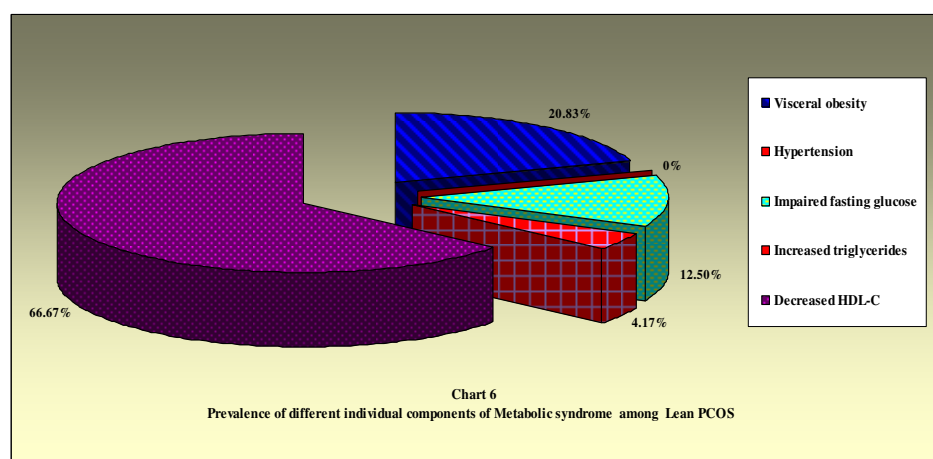


Fig 6 shows that among the individual components Dyslipidemia (Increased triglycerides and Decreased HDL-C) had the highest prevalence.

DISCUSSION

Metabolic Syndrome is now being increasingly recognized as an emerging threat which will invade desktops of public health policy planners in the decades to come. The clusters which make this syndrome and its etiopathogenesis keep getting varied in different ethnic populations, regions and countries. Factors like migration, socioeconomic status, lifestyle, nutrition habits play important role.

Therefore research in Metabolic Syndrome provides an interdisciplinary forum to explore the pathophysiology, recognition, and treatment of the cluster of conditions associated with the evolving entity of metabolic syndrome. These include but are not limited to: central obesity, endothelial dysfunction, insulin resistance, dyslipidemia, glucose intolerance, type 2 diabetes, prethrombosis and pro-inflammatory states, hyperinsulinemia, hyperuricemia, hypertension, cardiovascular disease, and PCOS.

Our results suggest that prevalence of MBS even in lean PCOS is higher (8.33%) compared to prevalence in USA (43 – 46%) [9] and Italy (8.2%) [10], which included both obese and non obese PCOS. Prevalence of MBS is doubled in lean PCOS than the controls (Refer chart 4). Prevalence of MBS in PCOS is 2.02 times higher than in the weight matched control population suggesting that in PCOS there is higher prevalence of MBS though not significantly different. Among the individual components we found that prevalence of dyslipidemia is higher than impaired glucose tolerance and visceral obesity and no person had hypertension.

Among the combination of individual components, we saw that visceral obesity and dyslipidemia had a higher prevalence; next is dyslipidemia and impaired fasting glucose and the least is visceral obesity and impaired glucose tolerance.

LIMITATIONS

One of the most important limitations of the study was small sample size (though the calculated sample size was only 18). Much larger group would have helped in better interpretation of the study.

CONCLUSION

Therefore early screening for the metabolic syndrome will gain particular benefit. Intervention with drugs such as metformin, may play a role in the future treatment of this condition, with a potential capacity to improve both metabolic and endocrine disturbances and risk of vascular disease.

The scarcity of converse data on the prevalence of metabolic syndrome among PCOS women with lean body mass index prompted this study. Criteria for defining metabolic syndrome include centripetal obesity, hypertension, fasting hyperglycemia, and dyslipidemia.

As expected MBS is more prevalent in lean PCOS compared to the controls and equals prevalence in Italian PCOS as well.

In spite of our limitations, our study focuses the MBS in lean PCOS, excluding obesity factor. With exclusion of confounding influence of obesity the pathophysiology underlying the authentic syndrome may be viewed as a separate entity. It is seen that obesity factor is just a modifier of the syndrome. Hence we suggest not only all PCOS women with obesity should be screened for MBS, even lean PCOS should be screened as well.

HUMAN ETHICS COMMITTEE CLEARANCE

The study was conducted in the department of physiology, PSG IMS&R after getting clearance from Institutions Human Ethics Committee, and after obtaining informed consent from the study and control group.

INFORMED CONSENT

The study was conducted after obtaining informed consent from the study and control group.

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**PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH,
COIMBATORE-4**
Institutional Human Ethics Committee Review Decision

Ref No : E090607-214

PROJECT TITLE:
Metabolic syndrome in lean patients with polycystic ovary syndrome- A case control study

NAME OF THE PRINCIPAL INVESTIGATOR
Dr. Malathi Balamurugan

REVIEW TYPE:
Regular: *Not applicable*
Exempt: ☒

DECISION:
Approved ☒ in the present form.

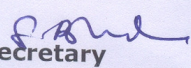
WAIVER OF CONSENT: *Not applicable*

Will be approved on submission of the following:-
Not applicable

Not approved in the present form. Suggested Modifications:-
Not applicable

VALIDITY OF THE APPROVAL: *One Year*

CONTINUING PANEL REVIEW:
Needed: *Not Applicable*
Not Needed: ☒


Secretary
(Institutional Human Ethics Committee)
9th, June 2007

